COMMENTS AND RESPONSE

Screening for Prostate Cancer

TO THE EDITOR: The U.S. Preventive Services Task Force's (USPSTF's) draft recommendation (1), which was based on Chou and colleagues' evidence review (2), gave prostate cancer screening a grade of "D" and thus concluded that "there is moderate or high certainty that [prostate cancer screening] has no net benefit or that the harms outweigh the benefits." We sympathize with the recommendations against current screening practices in the United States; however, Chou and colleagues' review (2) contained important errors of fact, interpretation, and statistics.

The largest trial of prostate-specific antigen (PSA) screening, the ERSPC (European Randomized Study of Screening for Prostate Cancer), has not yet reported prostate cancer mortality outcomes at its prespecified main follow-up time. To conclude that screening causes "small or no reduction in prostate cancer–specific mortality" (2) suggests that definitive conclusions of no benefit can be drawn from an ongoing trial with ambiguous results at interim follow-up. Furthermore, data on overall mortality from early follow-up of a screening trial cannot be used because screening trials lack the necessary statistical power to address this issue.

Of import, Chou and colleagues' conclusions seem based on the validity of the pooling in 2 meta-analyses. The 2 largest and highest-quality studies are the PLCO (U.S. Prostate, Lung, Colorectal and Ovarian Cancer) trial (3) and the ERSPC (4). However, PSA testing was widespread before the PLCO trial and in the control group throughout the study. Therefore, Pinsky and colleagues (5) stated that the PLCO trial "would not be able to answer the question of whether that level of opportunistic screening is conveying a mortality benefit over no screening." Contamination in the ERSPC was less than 15% (6). It is very hard to justify combining a trial of opportunistic versus systematic screening with a trial of systematic versus no screening and then calculate an "average" effect.

Chou and colleagues state that "48 men received treatment for every prostate cancer–specific death prevented" in the ERSPC. This is false. The number was calculated from the number of men diagnosed, not the number treated (4). Moreover, this statistic depends on the length of follow-up. Models have estimated this ratio to be approximately 20 at 12 years of follow-up in the ERSPC (7); the empirical estimate from the Göteborg trial (8) with 14 years of follow-up is 12.

In conclusion, fair-quality trials have demonstrated an ability of screening to prevent death from prostate cancer by 20% to 44% (4, 8). However, it is not unreasonable to recommend against the current method of PSA screening on the basis of the harms associated with overdiagnosis and risk for toxicity associated with treatment.

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Potential Conflicts of Interest: Dr. Lilja holds patents for free PSA, hK2, and intact PSA assays.

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TO THE EDITOR: I am disheartened by the publication of Chou and colleagues' recent review (1), which suggests that PSA screening is ineffective and harmful to U.S. men. I do not believe that the "exhaustive review of the latest evidence" described by the authors is applicable to these men.

The American Cancer Society (2) reports that 35 110 cases of prostate cancer are expected to occur in African American men in 2011 to 2012, accounting for 40% of all types of cancer diagnosed in this group. One in 5 African American men will be diagnosed with prostate cancer in his lifetime.

The average annual incidence rate for prostate cancer among African American men from 2003 to 2007 was 229.4 per 100 000 men—60% higher than in white men. African American men have the highest incidence rate in the world for this condition and are twice as likely to die of prostate cancer than white men. The 2010 U.S. Census shows that the racial distribution of the U.S. population is 79% for white persons, 13.8% for African Americans, 4% for Asians, and 12.5% for Hispanics.

In Chou and colleagues' review, the 7 articles chosen from the 379 articles that met inclusion criteria for determining the effectiveness of PSA screening shown in the Table are derived from predominantly white men of Northern or Western European heritage (predominantly Scandinavia). Several of the studies reanalyze the same cohorts or portions of previously reported cohorts. Thus, the data are mainly derived from the ERSPC and the PLCO study.

The latter study was the only one that included U.S. men and reported race or ethnicity. It included African Americans (4.5%), Asians (4.0%), Hispanics (2.1%), and Pacific Islanders or Native Americans (0.8%) and thus is not fully representative of the U.S. population. This study has often been criticized because of the contamination of the control group (men not having PSA testing in the

study), of whom 44% had PSA testing before enrollment and 52% of whom had PSA testing outside of the study during follow-up.

I remain unconvinced that these recommendations are applicable to anyone other than Scandinavian men older than age 50 years. Adopting these recommendations without considering the increasing racial diversity of the U.S. population seems unwise.

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Potential Conflicts of Interest: None disclosed.

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TO THE EDITOR: Although there is much to applaud in Chou and colleagues' review (1), their conclusions may do more harm than good. The authors have studied mortality as a primary end point. As an elderly urologist who spent almost half of his career in the pre-PSA testing era, I can personally attest to another and perhaps even more important factor that is being overlooked—that of patients with advanced prostate cancer.

I no longer see patients with bulky types of cancer that bleed and obstruct their urinary tracts. Many of these patients required emergency procedures and were left with permanent indwelling catheters. The patient presenting with diffuse painful osseous metastasis is now rare. Emergency orchiectomies plus radiation or surgical decompressions for impending paraplegia also seem less common.

These patients could live for years and still die of other diseases. They will not register as a success of PSA screening if only mortality is considered. In 1 study that evaluated the presence of metastasis as the primary end point, screened participants experienced a 48% reduction in the number of persons who developed metastatic disease (2).

The USPSTF has made some excellent points. The American Urological Association has modified its guidelines to account for the evidence as it has emerged. More judicious use of PSA screening and recommendations for treatment of early cancer are necessary. Better methods for distinguishing the types of cancer that are destined to spread or kill need to be developed. However, if the public at large interprets Chou and colleagues' conclusions as a condemnation of early diagnosis of prostate cancer by using PSA testing, we will be thrown back to the era when digital rectal examinations diagnosed dangerous types of cancer too late.

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IN RESPONSE: We appreciate the interest in our review. We would like to clarify that the purpose of the review was to synthesize the evidence on benefits and harms of prostate cancer screening, not to make recommendations about screening. The article was not written by the USPSTF but was commissioned and used by the USPSTF to inform its separate draft recommendation.

Dr. Carlsson and colleagues incorrectly state that the review's conclusions are based on the results of 2 published meta-analyses. In fact, our review reports and summarizes the results of the 2 major screening trials (ERSPC [1] and PLCO [2]) separately, with the range of potential benefits, as well as a discussion of the methodological limitations of the trials and potential reasons for discrepancies in their findings.

The number needed to treat of 48 was presented as reported by the ERSPC authors and was based on the number of patients who were diagnosed with prostate cancer and received such treatments as surgery, radiation therapy, and watchful waiting or active surveillance (the minimum standard of care). Excluding patients who received watchful waiting, the number needed to treat would be approximately 40. Finally, our article clearly described the duration of follow-up in the screening trials and noted that longer follow-up may be necessary to fully understand potential benefits of screening.

We agree with Dr. Hudson that robust data on benefits of screening in certain populations, such as African American men, are lacking. However, the large-scale randomized trials provide the current best evidence on potential benefits of screening. In addition, even though screening populations with a higher prevalence of prostate cancer may result in additional diagnoses, this would not necessarily result in greater benefits relative to harms because more men would also be subjected to harms related to diagnosis and treatment.

Dr. Feldstein points out that metastatic prostate cancer was not evaluated as an outcome in our review. Stage shift is considered an intermediate outcome to prostate cancer mortality and therefore not heavily weighted in USPSTF reviews. Fully understanding the effects of screening on metastatic prostate cancer would require assessment of the effects of metastatic disease on quality of life (which might be offset by negative effects related to treatment harms); however, such data were not provided in the screening trials.

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